

# Do new neurons have a functional role in the adult hippocampus?

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**Abstract** Although the existence of adult neurogenesis in the dentate gyrus is now almost universally accepted, it is not widely established that the new neurons perform any necessary function. However, evidence indicates that the number of new neurons that are generated and form functional synapses is clearly large enough to impact the circuitry of the hippocampus. Additionally, several treatments show parallel effects on neurogenesis and hippocampus-dependent behaviors, suggesting a possible causal relationship between new neurons and hippocampal function. Most importantly, several recent studies have found that killing or inhibiting proliferation of granule cell precursors impairs performance on several hippocampus-dependent tasks. Control experiments showing no impairment on slightly different behavioral tests suggest that the deficits are highly specific and unlikely to result from side effects of the neurogenesis-inhibiting treatments. In summary, the evidence to date strongly suggests that adult neurogenesis in the dentate gyrus plays a vital role in hippocampal function.

**Keywords** hippocampus · dentate gyrus · behavior · neurogenesis · granule cells

More than 40 years after it was first discovered, the fact that new neurons continue to be added to the dentate gyrus in adult mammals has become almost universally accepted [1, 14, 30]. Despite this growth in recognition that neurogenesis does in fact occur, there is still a great deal of uncertainty as to whether these new neurons play any real role in hippocampal function [44, 53]. One could argue that neurogenesis is not required for normal brain function, and that it instead represents a vestigial process left over from early development with no real function. However, there has been a substantial accumulation of indirect evidence that adult neurogenesis affects the functioning of the hippocampus. More importantly, a handful of recent studies provide direct evidence that neurogenesis does, in fact, play an important role in hippocampus-dependent behavior.

For adult neurogenesis to play a vital role in hippocampal function, it should show several key attributes. First, the process must generate enough new neurons to potentially impact the circuitry. Second, these new neurons must form proper connections with the existing hippocampal circuitry. Third, new neuron production should be increased by factors that improve learning and inhibited by factors that negatively impact hippocampus-dependent behavior. Finally, directly inhibiting adult neurogenesis should impair hippocampal function, whereas increasing neurogenesis should improve hippocampus-dependent abilities. We will discuss evidence for each of these below.

## Adult neurogenesis produces large numbers of long-lasting granule cells

It is unclear how many new neurons need to be produced to have an impact on the function of the dentate gyrus. Although the size of the granule cell population is quite

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large (2.4 million in rats and 0.98 million in mice [9, 86]), studies using immediate-early genes as markers of activated neurons show that spatial exploration activates ~35% of CA1 pyramidal neurons and ~25% of CA3 pyramidal neurons, but less than ~2% of granule cells [67]. This sparse activation of granule cells is thought to reflect sparse encoding in the dentate gyrus that in turn allows for large numbers of nonoverlapping memory traces [35, 75]. Because small numbers of granule cells are activated by a given experience, it follows that small numbers of new granule cells could potentially play an important role in dentate gyrus function. The number of young neurons in the dentate gyrus at a given time [13, 68] is relatively similar to the number of granule cells activated by behavior tasks [67, 85]. Approximately half of these young neurons survive to maturity in standard laboratory conditions [16], but hippocampus-dependent learning tasks can increase their survival [29, 42, 62]. Taken together, these findings seem to indicate that there are enough new neurons to potentially affect hippocampal function.

### New neurons integrate into the hippocampus

For new granule cells to function as neurons, they must integrate into the hippocampal network. This condition is necessary, although it is not, of course, sufficient to demonstrate that they serve a behavioral function. Activation of new granule neurons by physiologically appropriate stimuli has not yet been demonstrated, as it has in the birdsong system [66]. However, several recent studies using acute slice preparations have shown that new granule cells do have functional synapses. The earliest active synaptic inputs onto new granule cells are those responsive to GABA, which is excitatory in the young granule cells as it is in the developing brain [3, 24, 28, 36, 64, 65, 80]. Functional glutamatergic synapses appear after GABAergic synapses [24, 28, 72]. The specific timing of development of synapses has been examined in retrovirally labeled granule cells, where synaptic GABAergic responses could be evoked in approximately 50% of 7-day-old granule cells, and synaptic glutamatergic responses could be evoked in approximately 65% of 14-day-old granule cells [28]. Interestingly, synaptic responses in young granule cells are more easily potentiated than those in older granule cells [72, 76]. Young granule cells extend axons into the CA3 region [32, 33] and fire action potentials [64, 83]. The technical difficulty associated with finding synaptically paired granule cells and CA3 pyramidal cells has made it impossible so far to examine synaptic output of young granule cells. However, the extension of axons by and development of synapses onto new granule cells suggests

that they do become fully integrated into the network, probably within 4 to 5 weeks of their birth.

### Parallel effects on neurogenesis and learning/memory

If new granule neurons play an important role in hippocampal function, then it follows that gain or loss of new neurons should alter function. However, there are two issues that make this idea less than straightforward to test. The first is that the function of the hippocampus itself is still under debate (see text box), and the function of the dentate gyrus specifically in most tasks is unclear. Second, the relationship between the function of a given neuronal population and the number of neurons in that population is not likely to be linear. Lesion studies show that near-complete removal of the hippocampus is required to produce detectable impairment in several hippocampus-dependent tasks, so even if the loss of a considerable number of new neurons does not produce an effect, this does not mean they are not functional. Conversely, adding more new neurons might not significantly improve hippocampal function, because the dentate gyrus may normally produce all of the new neurons it needs to function optimally or because other brain regions involved in a given task limit behavioral improvement.

Nonetheless, evidence for parallel effects on the rate of neurogenesis and behavior in learning and memory tasks in several experimental paradigms is at least consistent with a causal relationship (also see discussion by [41]). Mouse strains that have higher numbers of new granule cells learn better in the Morris water maze [37], and wild-living rodent strains with higher rates of neurogenesis use more spatially complex arrangements of food storage sites and are better at learning a rewarded place learning task [7, 27]. In both of these cases, the rates of adult neurogenesis may reflect changes to granule cell precursors during development, so it is possible that developmental changes are responsible for the differential spatial abilities. However, similar changes are also seen after several experimental manipulations that begin in adulthood. Wheel running and housing enrichment both increase neurogenesis and improve learning. Voluntary and forced wheel running increase granule cell precursor proliferation [10, 21, 25, 40, 79, 81, 82], and improve performance on hippocampus-dependent memory tasks [4, 26, 82]. Exercise also appears to alleviate symptoms of depression in humans, consistent with a link between neurogenesis and depressive illness [23]. Similarly, housing in an enriched environment increases young granule cell survival and improves learning in several tasks [38, 60]. However, situations have been found in which the effects of these manipulations on learning and neurogenesis can be dissociated: mice bred for increased running show high

### The function of the hippocampus

That the hippocampus plays a role in certain forms of learning and memory has been apparent since the initial reports of severe amnesia in patient H.M. [51]. Following bilateral removal of the medial temporal lobes that included the majority of his hippocampal formation, H.M. became severely impaired in his ability to create new episodic, or autobiographical, memories, although he retained his ability to complete tasks requiring recall from working and procedural memory [52]. Several other patients with similar memory impairments following hippocampal damage or atrophy have since been documented [78]. The initial attempts to develop animal models failed to demonstrate a similar form of memory impairment after hippocampal damage in rats and monkeys, but it was not clear whether this reflected a very different role for the hippocampus in non-human species or a lack of suitable, e.g., non-verbal, tests [34]. It was not until the development of spatial memory tasks that the effects of hippocampal lesions in rodents began to emerge [58], leading to the idea that in rodents, the hippocampus primarily subserves memory for places [12, 59, 61]. Further support for an important role of the hippocampus in spatial memory comes from the fact that the hippocampus contains neurons, so-called “place cells”, that respond to spatial locations [43]. However, strong evidence now points to the involvement of the rodent hippocampus in several forms of completely non-spatial associative memory [2, 31, 48], and suggest that the primary role of the hippocampus in all mammalian species may be to rapidly encode sequences of events [22, 57]. In addition to its role in episodic and spatial memory, several lines of evidence suggest that the hippocampus may also play a role in depressive illness [19, 71].

levels of neurogenesis but no learning improvement [69], whereas enrichment-induced changes in an anxiety test, novelty-suppressed feeding, and in spatial learning in the Morris water maze are observed even in the absence of new granule cells [50].

Stress and soft-food diets both inhibit neurogenesis and impair hippocampus-dependent learning. Stress and stress hormones strongly inhibit granule cell birth and decrease survival (reviewed in [54]) and impair hippocampus-dependent learning [39, 41, 45]. Interestingly, soft-food diets and the resulting decrease in chewing also lead to decreased neurogenesis [5, 55] and impaired hippocampus-dependent learning [47, 63], possibly resulting from decreased cerebral blood flow and release of growth factors into the brain.

Aging also decreases neurogenesis and is associated with impairment in hippocampus-dependent learning. Decreased cell proliferation and reduced numbers of immature neurons are associated with deficits in hippocampus-dependent behavior in old rats [84]. Two studies have found significant correlations between cell proliferation and spatial learning within the same group of rats [17, 18]. However, other studies have found no correlation, or even a negative correlation, between neurogenesis and learning in aged rats [8, 15, 49]. Because of the differences in the timing of cell labeling with regard to behavioral testing and in the age of the cells examined (i.e., cells dividing after learning versus very young neurons versus mature neu-

rons), these studies are not necessarily inconsistent with each other but do suggest a complex relationship between neurogenesis and hippocampal function in aged animals.

Although the large number of these associations is suggestive of a relationship between neurogenesis and hippocampal function, these correlations provide no direct evidence of a causal relationship between new neurons and behavior. Many of the manipulations have known effects in other brain regions, such as neocortex (e.g., enriched environment and soft-food diet), that contribute to performance even on “hippocampus-dependent” behavior tasks. Others (e.g., stress) have almost immediate effects on hippocampus-dependent learning, which are not likely to result from changes in neurogenesis. Strong evidence for a causal relationship between neurogenesis and hippocampal function can come only from manipulations that directly and specifically alter the production or activation of new granule cells.

### Functional effects of killing neuronal precursors

Two approaches have been used to directly address the function of new neurons in the adult hippocampus. Both eliminate new neurons by preventing their birth. The chemical antimitotic agent methylazoxymethanol acetate (MAM) reversibly stops granule cell precursors from dividing. However, it also inhibits cell division indiscriminately.

inately throughout the rest of the brain as well as in the body when given systemically as in these studies. Presumably because of these nonspecific effects, MAM can cause weight loss, decreased locomotor activity, and piloerection/dirty fur associated with stress and poor health [20, 74]. Ionizing radiation kills dividing granule cell precursor cells [89]. Direct effects on other dividing cells can be confined to the head and even, with shielding, to a vertical or horizontal slab within the brain that contains the hippocampus. However, even when irradiation is confined to the head, it causes weight loss [77], which may reflect overall ill health that could potentially cause behavior changes unrelated to loss of new granule cells. Additionally, irradiation can cause hippocampal inflammation, possibly resulting from or causing damage to other hippocampal cells [56]. However, small changes to the treatment regimens for both methods can minimize these side effects. When used at low dose, MAM kills 75% of granule cell precursors without causing weight loss or other outward signs of general ill-health [73, 74]. Likewise, the inflammation associated with irradiation can be avoided by choosing barbiturate anesthetics rather than ketamine during the irradiation procedure [89]. Although side effects may not be completely eliminated even with these modified procedures, potential nonspecificity can also be controlled for experimentally by showing normal performance on tasks that require similar sensory and motor skills but make different demands on the hippocampus. As described

below, impairment is not found in delay eyeblink classical conditioning (using MAM), simple context fear conditioning (MAM), or Morris water maze acquisition (irradiation), arguing that these treatments do not cause widespread, nonspecific behavioral effects. Therefore, although it is very difficult to completely rule out the possibility of nonspecific treatment effects, when side effects are minimized and controlled for, MAM and irradiation are both good tools for directly addressing the question of new granule neuron function (Table 1).

Shors et al. [73, 74] gave low-dose MAM for 2 weeks, which resulted in a 75% loss of granule cell birth. They found that MAM-treated rats were impaired on two hippocampus-dependent learning and memory tasks: trace eyeblink conditioning and trace cued fear conditioning. Importantly, the nonhippocampus dependent “delay” version of the eyeblink task, which differs only in the temporal association of the conditioned and unconditioned stimuli, was unaffected. Delay-dependent effects have also been found in the novel object recognition and nonmatch to sample tests. Decreased memory for a novel object was seen in MAM-treated animals at 24- or 48-h delay time points [11], while no impairment was seen in MAM- or irradiation-treated animals after 15-min or 1-h delay [11, 46]. Similarly, irradiated rats were impaired on a delayed nonmatch-to-sample cued water maze task with 2- and 4-min delay times, but not with 0- or 1-min delay [88]. These delay-dependent effects are typical of hippocampal deficits; effects of

**Table 1** Experiments testing the behavioral effects of loss of new granule neurons in the adult hippocampus

Task	Details	Impaired	Method	Control task <sup>a</sup>	Reference
Trace eyeblink classical conditioning		Yes	MAM, 5 mg/kg× 14 days	Delay version of task	[74]
Trace-cued fear conditioning		Yes	MAM, 7 mg/kg× 14 days	–	[73]
T-maze place recognition	90 s delay	Yes	IRR, 3 Gy×8 days	Novel object recognition (15 min delay)	[46]
Novel object recognition	1–2 days delay	Yes	MAM, 5 mg/kg× 14 days	Same task with 1 h delay	[11]
Delayed nonmatch to sample	2–4 min delay	Yes	IRR, 7.5 or 10 Gy× 2 days	Same task with 0 or 1 min delay	[88]
Contextual fear conditioning	Transparent chamber	Yes	IRR, 7.5 or 10 Gy× 2 days	Cued fear conditioning	[88]
Contextual fear conditioning	Closed chamber	No	MAM, 7 mg/kg× 14 days	–	[73]
Morris water maze, acquisition		No	MAM and IRR (see refs)	–	[46, 50, 73, 77]
Morris water maze, long-term memory		Yes	IRR, 10 Gy×2 days	MWM acquisition; long-term memory in cued task	[77]
Novelty-suppressed feeding (anxiety/depression)		No	IRR, 5 Gy×3 days, ketamine	–	[50, 70]

<sup>a</sup> Control task indicates similar task that showed no impairment in the same study.



complete hippocampal lesion are usually only evident in tasks with long retention times [31, 87]. Performance in contextual fear conditioning was impaired by loss of young granule cells in one study [88], but not in another [73]. These two studies used different methods of decreasing neurogenesis (irradiation and MAM, respectively), but it has been suggested that a more important difference may be the use of external cues to make the context complex and increase the demand on the hippocampus [88]. In a hippocampus-dependent test of anxiety-like behavior, novelty-suppressed feeding, irradiation had no effect on behavior, but did prevent antidepressants from altering behavior in this task [50, 70], suggesting that new neurons do not play a primary role in anxiety-like behavior, but may affect performance of this task under some conditions. Spatial memory has been shown to be impaired in a place recognition T-maze task [46]. Interestingly, no impairment has been found with either MAM or irradiation in spatial learning in the classic Morris water maze task [46, 50, 73, 77]. However, one study went further, testing long-term memory for the platform location at several delay intervals, and found that control rats showed no decline in memory for the platform location following a 2-week retention interval, while irradiated rats' performance dropped to chance levels [77].

Taken together, these MAM and irradiation studies indicate that new neurons are required for at least some aspects of hippocampal function. Behavioral impairment has been found in a wide variety of both spatial and nonspatial hippocampus-dependent tasks. In nearly all cases, the versions of tasks showing no deficit—delay eyeblink conditioning, short-delay nonmatch to sample, short-delay novel object recognition, and simple context fear conditioning—do not require an intact hippocampus, while tasks requiring the hippocampus are impaired by loss of new neurons. That is, loss of new neurons has the same effect as loss of the entire hippocampus in these tasks. One finding appears to be an exception to this rule [77], and is therefore particularly interesting. Only long-term reference memory for, and not acquisition of, platform location was found to be impaired in irradiated rats, even though acquisition in the Morris water maze requires the hippocampus [6]. This dissociation may provide the first hint at the specific role of the new neurons within the hippocampus. Although this specific role is not yet clear, the impairments found in several studies, using two different methods to inhibit neurogenesis and several different behavior tasks, clearly indicate an important role for new granule neurons in learning and memory.

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